SPEB2-39 variants of cysteine protease in Example 1, page 8, and Table 1, pages 9-18 (see also Kapur et al. 1993). New claims 18 and 19 claim specifically that the mammal is a human. Specific for this can be found on page 8, in that the vaccine can be administered to a human. In light of this support, the amendments do not add new matter.

Outstanding Issues:

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner had rejected Claims 1 and 2 as being indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as their invention. Claim 2 has been deleted. The Applicants respectfully assert that one of ordinary skill in the art would understand what is claimed to be the subject matter which the Applicants regard as their invention in the light of the amendments to Claim 1 and the following remarks.

The Examiner states that the recitation of "an amount sufficient to confer immunity to Group A streptococcal infection" is vague and indefinite as to the metes and bounds of the words "amount" and "sufficient". As discussed in the recent phone interview, a sufficient amount of a vaccine can readily be determined by one of skill in the art. The art states that, "The recommended doses of vaccines are derived from theoretical considerations, experimental trials and experience" (1991 Red Book: Report of the Committee on Infectious Diseases.1991. 22nd Ed. Elk Grove Village, IL: American Academy of Pediatrics, page 20). The courts have in fact held that determining a dose curve is "nothing more than routine" (Merck & Co., 10 USPQ 2d 1847). Theoretical considerations for determining a dose curve include such factors as age and weight of a subject. These considerations vary between subject. Thus the doses vary and are most clearly defined by stating that the amount is sufficient to produce the desired effect. However, in the interest of advancing the prosecution, the Applicants have amended Claim 1 so that it no longer includes the recitation "amount sufficient". The Applicants respectfully request the Examiner to reconsider the rejection of Claim 1.

Rejection under 35 U.S.C. § 102(b)

The Examiner has rejected Claims 1-4 as being anticipated by Tai et al., or Hauser et al., or Gerlach et al. The Examiner states that the distinguishing features of the invention are not recited in the claims and thus the claims are not distinguished over the prior art. The

Applicants have deleted Claim 2 and amended Claims 1, 3 and 4. The amendments more clearly distinguish the invention over the prior art by indicating that the claimed invention is a vaccine comprising only the cysteine protease variants SPEB2 through 39 taught by the Applicants.

In light of the amendments, the Applicants assert that Gerlach et al., Tai et al., and Hauser et al. do not anticipate the invention of the Claims 1, 3 and 4, because they do not teach purified SPEB 2 through 39. Gerlach et al. teaches the purification of proteins of molecular weights, 44, 30, and 12 kDa. These proteins are not the same molecular weights as the proteins of the present invention and thus they are not SPEB 2 through 39 (40 and 27 kDa). In support of this conclusion, Gerlach et al. states that "the B-toxin and streptococcal proteinase precursor represent one and the same protein" (page 228). The sequence for "streptococcal proteinase" was previously determined by Tai et al. and is 34 amino acids smaller than SPEB2 through 39. Thus the purified proteins taught by Gerlach et al. and Tai et al. do not anticipate Claims 1-4. Hauser et al. only teach the purified SPEB1 variant and do not teach SPEB 2 through 39. The purified cysteine proteases of Gerlach et al., Tai et al. and Hauser et al. do not have the same structures as purified cysteine proteases, SPEB 2 through 39, claimed by the Applicants (Kapur et al. 1993). Thus, the amended Claims 1, 3 and 4 are patentably distinguishable over the prior art as they do not teach all of the claims limitations and the Applicants respectfully request the Examiner to reconsider the rejection of Claims 1, 3 and 4 (Verdegaal Bros. V. Union Oil Co. of California 814 F.2d 628, 2 USPQ2d (BNA) 1051, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d (BNA) 1913).

Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected Claim 5 as being unpatentable over Tai et al., or Hauser et al., or Gerlach et al., in view of Abe et al. The Applicants have amended independent Claims 1 and 3 from which Claim 5 depends. The Applicants assert that the claimed invention as a whole, is not *prima facie* obvious to one of ordinary skill in the art at the time because the references do not teach or suggest all the claim limitations and there is no reasonable expectation of success or suggestion to combine the references.

The Applicants assert that the combined references do not teach examples of purified SPEB2 through 39 as discussed previously. Thus, Tai et al., or Hauser et al., or Gerlach et al., in view of Abe et al. do not teach all of the claim limitations and the claimed invention as a

whole, would not have been *prima facie* obvious to one of ordinary skill in the art at the time (In re Royka, 490 F.2d 981, USPQ 580 (CCPA 1974).

In addition, Applicants assert that while the references do teach that SPEA and SPEB are superantigens, this information would not provide a suggestion to combine the references or a reasonable expectation of success in making a cysteine protease vaccine capable of conferring immunity to *Streptococcus pyogenes* (In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Examiner states that one of ordinary skill in the art would have a reasonable expectation of success and derive motivation to combine a cysteine protease with an M protein vaccine from the teachings of Abe et al. in regards to the similarity between streptococcal M protein, SPEA, and SPEB. The similarity relied upon is that they are superantigens and thus "induce selective expansion of T cells" which would be expected to lead to immunity in patients to streptococcal Group A infections. To the contrary, the Applicants assert that one of ordinary skill in the art would realize that the expansion of T cells induced by superantigens would not lead to immunity. The plain meaning of superantigens is antigens,

> **...Which have a distinctive mode of binding that enables them to stimulate very large numbers of T cells, often with disastrous consequences.... This mode of stimulation is not specific for the pathogen and thus does not lead to adaptive immunity but to massive production of cytokines by CD4 T cells, the predominant responding population. These cytokines have two effects on the host: systemic toxicity and suppression of the adaptive immune response. Both of these effects contribute to microbial pathogenicity (Immunobiology 1994. London, UK: Current Biology Ltd. Section 4-24, underline added for emphasis by Applicants).**

Thus, superantigens are commonly known not to induce antigen specific immune responses, which would be required for a vaccine, but instead to act primarily as virulence factors. In fact, the prior art teaches away from using streptococcal superantigens in a vaccine with the following statement, "superantigens can elicit the non-specific proliferation of a substantial portion of the T-cell population and this could have serious consequences for the host. Therefore, like HCR antibody epitopes, regions of M proteins that might be responsible for these mitogenic activities would need to be omitted from a vaccine." (Kehoe et al., Immunol. Today, 1992, page 365). Thus the claims **are not** *prima facie* obvious because there is no suggestion

to combine the references and there is no reasonable expectation of success as the references and the common art teach away from the claimed invention (In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed Cir. 1992), W. L. Gore & Assoc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983)). The Applicants respectfully request the Examiner to reconsider the rejection of Claim 5.

Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 6-17 over Fischetti et al., and Kehoe in view of Tai et al., or Hauser et al., or Gerlach et al., and in further view of Abe et al. The Applicants assert that the claimed invention as a whole, is not *prima facie* obvious to one of ordinary skill in the art at the time because there is no suggestion or motivation provided to combine the references. Furthermore, even if the references were combined, Applicant's invention would still not be *prima facie* obvious because there would not be a reasonable expectation of success for combining the references (W. L. Gore & Assoc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983)).

The Examiner states that motivation to combine the references would be derived from the knowledge that conserved cysteine proteases are found in all isolates of Streptococcus and to the general suggestion by Kehoe that a multivalent vaccine would be more effective. The Examiner refers to the suggestion by Kehoe that the field should "explore possible solutions to limitations associated with designing multivalent, type-specific epitope vaccines" in regard to the "design of effective vaccines to protect against a limited range of M types". It would be clear to one of ordinary skill in the art, that this refers to combining multiple types of M-proteins to produce a multivalent vaccine against a range of M types. These statement makes no suggestion of using purified cysteine proteases or any streptococcal protein other than M protein in a vaccine against Group A streptococcal infections. In the event that this statement was misinterpreted to include proteins other than M types, it is at best a general suggestion to "explore possible solutions". It is well established that even when on considers an invention to be "obvious to try" in light of "only general guidance as to the particular form of the invention", the invention is not rendered obvious (In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988), In re Tomlinson, Hall, and Geigle, 150 USPQ 623, 626 (CCPA 1966)).

In addition, the Applicants assert that the references teach examples of cysteine proteases that are superantigens, this information teaches away from making a cysteine protease vaccine capable of conferring immunity to *Streptococcus pyogenes* as discussed previously. More specifically, Kehoe in view of Abe et al. teaches away from the present invention with the following statement, "superantigens can elicit the non-specific proliferation of a substantial portion of the T-cell population and this could have serious consequences for the host. Therefore, like HCR antibody epitopes, regions of M proteins that might be responsible for these mitogenic activities would need to be omitted from a vaccine." (Kehoe, page 365). Thus, one of ordinary skill in the art would be discouraged from using a cysteine protease in a vaccine as they would not be assured of a reasonable expectation of success (W. L. Gore & Assoc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983)). The Applicants respectfully request the Examiner to reconsider the rejection of Claims 6-17.

As discussed in the recent phone interview, the Applicants request that the Examiner also consider the long felt need for a Group A streptococcal vaccine (Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)). At the time of the invention and to date, an effective vaccine for humans has not been FDA approved. Thus, Kehoe stated that "Despite the fact that highly protective antigens were first identified almost seventy years ago, group A streptococci continue to feature on lists of important human pathogens for which no effective vaccine is currently available"(Kehoe et al, page 362). Thus, a long felt need for a Group A streptococcal vaccine has not been satisfied to date. The Applicant's invention overcomes the major limitation of type-specificity inherent in the current M protein vaccines and thus would satisfy this long felt need. The Applicants respectfully request the Examiner to reconsider the rejection of Claims 6-17.

CONCLUSIONS

Entry of the amendments to the claims before examination of the application is respectfully requested. Claim 2 has been deleted and Claims 1, 3-6, 10, and 12 have been amended. Claims 1, and 3-17 are pending in this application.

In light of the amendments and remarks, the Applicants respectfully request that the rejections to the claims be reversed and a Letter Patent be issued on the application. If there are

any questions regarding this Amendment and Response or the application in general, please do not hesitate to contact the undersigned.

Please charge additional fees to Account No. 06-2375, under Order No. 09507112, from which the undersigned is authorized to draw.

Respectfully submitted,

Date: March 19, 2001

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Pending claims:

1. (Amended three times) A vaccine comprising:

a physiologically acceptable non-toxic vehicle containing a purified cysteine protease, which confers immunity to a mammal against Group A streptococcal infection, selected from the group consisting of SPEB2, SPEB3, SPEB4, SPEB5, SPEB6, SPEB7, SPEB8, SPEB9, SPEB10, SPEB11, SPEB12, SPEB13, SPEB14, SPEB15, SPEB16, SPEB17, SPEB18, SPEB19, SPEB20, SPEB21, SPEB22, SPEB23, SPEB24, SPEB25, SPEB26, SPEB27, SPEB28, SPEB29, SPEB30, SPEB31, SPEB32, SPEB33, SPEB34, SPEB35, SPEB36, SPEB37, SPEB38, and SPEB39.

3. (Once amended) The vaccine of claim 1, wherein said cysteine protease is a mutant thereof or synthetic peptide thereof.

4. (Once amended) The vaccine of claim 1 or claim 3, wherein said infection is selected from the group consisting of pharyngitis, tonsillitis, skin infections, acute rheumatic fever, scarlet fever, post-streptococcal glomerulonephritis, and toxic-shock-like syndrome.

5. (Once amended) The vaccine of claim 1 or claim 3, further comprising a purified streptococcal M protein antigen.

6. (Once amended) A method of immunizing mammals comprising:

administering to a mammal a vaccine comprising, a purified cysteine protease, synthetic peptide thereof, or mutant thereof, in an amount sufficient to confer immunity to a Group A streptococcal infection.

7. The method of claim6, wherein said vaccine is given by parenteral administration.

8. The method of claim 7, wherein said parenteral administration is selected from the group consisting of subcutaneous administration and intramuscular administration.

9. The method of claim 6, wherein said vaccine is administered orally.

10. (Once amended) The method of claim 6, wherein said infection is selected from the group consisting of pharyngitis, tonsillitis, skin infections, acute rheumatic fever, scarlet fever, post-streptococcal glomerulonephritis, sepsis, and toxic-shock-like syndrome.

12. (Once amended) The method of claim 6 further comprising:

administering to the mammal a purified streptococcal M protein antigen.

13. The method of claim 12, wherein said vaccine is given by parenteral administration.

14. The method of claim 13, wherein said parenteral administration is selected from the group consisting of subcutaneous administration and intramuscular administration.

15. The method of claim12, wherein said vaccine is administered orally.

16. The method of claim 12, wherein said infection is selected from the group consisting of pharyngitis, tonsillitis, skin infections, acute rheumatic fever, scarlet fever, post-streptococcal glomerulonephritis, sepsis, and toxic-shock-like syndrome.

17. The method of claim 12, wherein said vaccine is administered in multiple doses.

18. The vaccine of claim 1, wherein said mammal is a human.

19. The method of claim 6, wherein said mammal is a human.